Amendments to the Claims

Please cancel Claims 1-51, 56, 59-65, 93 and 95-102. Claims 52-55, 57, 66-71, 73, 80, 82, 92 and 94 are amended. Please add new Claims 103-134. The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing

1-51. (Cancelled)

52. (Withdrawn-currently amended) A transfectoma comprising nucleic acids encoding a human heavy chain and a human light chain, wherein the transfectoma produces a detectable amount of the antibody of claim ~~1~~ 103.

53. (Withdrawn-currently amended) A transfectoma which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in ~~SEQ ID NOs:1, 5, or 9 and SEQ ID NOs:3, 7, or 11~~ SEQ ID NO:1 or 5 and SEQ ID NO:3 or 7, respectively[[,]] ~~and conservative sequence modifications thereof~~.

54. (Withdrawn-currently amended) A transfectoma which produces a human monoclonal antibody having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences as set forth in ~~SEQ ID NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or 12~~ SEQ ID NO:2 or 6 and SEQ ID NO:4 or 8, respectively[[,]] ~~and conservative sequence modifications thereof~~.

55. (Withdrawn-currently amended) A eukaryotic or prokaryotic host cell which produces a human monoclonal antibody having heavy chain and light chain variable regions which comprise the amino acid sequences as set forth in ~~SEQ ID NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or 12~~ SEQ ID NO:2 or 6 and SEQ ID NO: 4 or 8, respectively[[,]] ~~and conservative sequence modifications thereof~~.

56. (Cancelled)

57. (Withdrawn-currently amended) A method of producing a human monoclonal antibody which binds to human CD20, comprising:

immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with human CD20 or a cell expressing human CD20, such that antibodies are produced by B cells of the animal;

isolating B cells of the animal;

fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies specific for human CD20; and

isolating the human monoclonal antibodies specific for CD20 from the culture supernatant of the hybridoma, or the transfectoma derived from such hybridoma;

wherein said human monoclonal antibody which binds to human CD20 comprises a heavy chain variable region and a light chain variable region, wherein said heavy chain variable region comprises complementarity determining region 3 (V_H CDR3) having the amino acid sequence set forth in SEQ ID NO:15.

58. (Withdrawn) A method according to claim 57, wherein the immunization is performed with cells which have been transfected with human CD20.

59.-65. (Cancelled)

66. (Withdrawn-currently amended) The antibody according to claim ~~1~~ 103, further comprising a chelator linker for attaching a radioisotope.

67. (Withdrawn-currently amended) An immunoconjugate comprising an antibody according to claim ~~1~~ 103 linked to a cytotoxic agent, a radioisotope, or a drug.

68. (Withdrawn-currently amended) A bispecific molecule comprising an antibody according to claim ~~1~~ 103 and a binding specificity for a human effector cell.

69. (Withdrawn-currently amended) A bispecific molecule comprising an antibody according to claim ~~1~~ 103 and a binding specificity for a human Fc receptor or a binding specificity for a T cell receptor, such as CD3.

70. (Withdrawn-currently amended) A method of inhibiting growth of a cell expressing CD20, comprising contacting the cell with an effective amount of an antibody according to claim ~~1~~ 103 such that the growth of the cell is inhibited.

71. (Withdrawn-currently amended) A method of killing a cell expressing CD20, comprising contacting the cell with the antibody of claim ~~1~~ 103, such that killing of the cell expressing CD20 occurs.

72. (Withdrawn) The method of claim 70, wherein the cell is a B lymphocyte or a tumor cell.

73. (Withdrawn-currently amended) A method of treating or preventing a disease or disorder involving cells expressing CD20, comprising administering to a subject a human antibody according to claim ~~1~~ 103, in an amount effective to treat or prevent the disease.

74. (Withdrawn) The method of claim 73, wherein the disease is a B cell lymphoma.

75. (Withdrawn) The method of claim 73, wherein the disease is B cell non-Hodgkin's lymphoma.

76. (Withdrawn) The method of claim 73, wherein the disease is selected from the group consisting of precursor B cell lymphoblastic leukemia/lymphoma and mature B cell neoplasms, such as B cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), cutaneous follicle center lymphoma, marginal zone B cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenström's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).

77. (Withdrawn) The method of claim 76, wherein the disease is follicular lymphoma (FL).

78. (Withdrawn) The method of claim 76, wherein the disease is B cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

79. (Withdrawn) The method of claim 73, wherein the disease is selected from the group consisting of lymphomatoid granulomatosis, primary effusion lymphoma, intravascular large B cell lymphoma, mediastinal large B cell lymphoma, heavy chain diseases (including γ, μ, and α disease), lymphomas induced by therapy with immunosuppressive agents, such as cyclosporine-induced lymphoma, and methotrexate-induced lymphoma.

80. (Withdrawn-currently amended) A method of treating or preventing an immune disease involving CD20 expressing immune cells, comprising administering to a subject the antibody of claim ~~1~~ 103, in an amount effective to treat or prevent the immune disease.

81. (Withdrawn) The method of claim 80, wherein treatment includes the killing of B cells which produce antibodies against autoantigens.

82. (Withdrawn-currently amended) The method of claim 73, wherein the disease or disorder is selected from the group consisting of psoriasis, psoriatic arthritis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomerulonephritis, eczema, asthma, atherosclerosis, leukocyte adhesion deficiency, multiple sclerosis, Raynaud's syndrome, Sjögren's syndrome, juvenile onset diabetes, Reiter's disease, Behçet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathies, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Omenn's syndrome, chronic renal failure, acute infectious mononucleosis, and HIV [[,]] ~~and~~ or herpes virus associated diseases.

83. (Withdrawn) The method of claim 82, wherein the autoimmune disease is rheumatoid arthritis (RA).

84. (Withdrawn) The method of claim 73, wherein the disease is an inflammatory, immune and/or autoimmune disorder selected from ulcerative colitis, Crohn's disease, juvenile onset diabetes, multiple sclerosis, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, systemic sclerosis, and pemphigus vulgaris.

85. (Withdrawn) The method of claim 73, wherein the disease is an inflammatory, immune and/or autoimmune disorder selected from inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, and multiple sclerosis.

86. (Withdrawn) The method of claim 70, further comprising separately administering another therapeutic agent to the subject.

87. (Withdrawn) The method of claim 86, wherein the therapeutic agent is a cytotoxic agent or a radiotoxic agent.

88. (Withdrawn) The method of claim 86, wherein the therapeutic agent is an immunosuppressant.

89. (Withdrawn) The method of claim 86, wherein the therapeutic agent is an immunological modulating agent, such as a cytokine or a chemokine.

90. (Withdrawn) The method of claim 86, wherein the therapeutic agent is selected from the group consisting of doxorubicin, cisplatin, bleomycin, carmustine, chlorambucil, and cyclophosphamide.

91. (Withdrawn) The method of claim 86, wherein the therapeutic agent is selected from the group consisting of anti-CD25 antibodies, anti-CD19 antibodies, anti-CD21 antibodies, anti-CD22 antibodies, anti-CD37 antibodies, anti-CD38 antibodies, anti-IL6R antibodies, anti-IL8 antibodies, anti-IL15 antibodies, anti-IL15R antibodies, anti-CD4 antibodies, anti-CD11a antibodies, anti-alpha-4/beta-1 integrin (VLA4) antibodies, CTLA4-Ig, and anti-C3b(i) antibodies.

92. (Withdrawn-currently amended) An *in vitro* method for detecting the presence of CD20 antigen, or a cell expressing CD20, in a sample comprising:

contacting the sample with the antibody of claim ~~1~~ 103 under conditions that allow for formation of a complex between the antibody and CD20; and

detecting the formation of a complex.

93. (Cancelled)

94. (Withdrawn-currently amended) An *in vivo* method for detecting CD20 antigen, or a cell expressing CD20, in an subject comprising:

administering the antibody of claim ~~1~~ 103 under conditions that allow for formation of a complex between the antibody and CD20; and detecting the formed complex.

95.-102. (Cancelled)

103. (New) An isolated human monoclonal antibody which binds to human CD20, comprising a heavy chain variable region and a light chain variable region, wherein said heavy chain variable region comprises complementarity determining region 3 (V_H CDR3) having the amino acid sequence set forth in SEQ ID NO:15.

104. (New) The antibody of Claim 103, wherein each of the heavy chain variable region and the light chain variable region comprises three CDRs, wherein the heavy chain variable region contains the V_H CDRl of SEQ ID NO:13 and the V_H CDR2 of SEQ ID NO:14, and wherein the light chain variable region contains the V_L CDRl of SEQ ID NO:16, the V_L CDR2 of SEQ ID NO:17 and the V_L CDR3 of SEQ ID NO:18.

105. (New) The antibody of Claim 103, wherein each of the heavy chain variable region and the light chain variable region comprises three CDRs, wherein the heavy chain variable region contains the V_H CDRl of SEQ ID NO:19 and the V_H CDR2 of SEQ ID NO:20,

and wherein the light chain variable region contains the V_L CDRl of SEQ ID NO:22, the V_L CDR2 of SEQ ID NO:23 and the V_L CDR3 of SEQ ID NO:24.

106. (New) The antibody of Claim 103, wherein the antibody is an IgG1 antibody.

107. (New) The antibody of Claim 103, wherein the antibody dissociates from human CD20 with a dissociation rate constant (k_d) of about 10^{-5} sec^{-1} or less.

108. (New) The antibody of Claim 103, wherein the antibody binds to human CD20 with an affinity constant (K_D) of about 5 nM or less.

109. (New) The antibody of Claim 103, wherein said antibody is encoded by human heavy chain nucleic acid comprising the variable region nucleotide sequence of SEQ ID NO:1.

110. (New) The antibody of Claim 103, wherein said antibody is encoded by human heavy chain and human kappa light chain nucleic acids comprising the nucleotide sequences in their variable regions as set forth in SEQ ID NO:1 and SEQ ID NO:3, respectively.

111. (New) The antibody of Claim 103, wherein said antibody is encoded by human heavy chain nucleic acid comprising the variable region nucleotide sequence of SEQ ID NO:5.

112. (New) The antibody of Claim 103, wherein said antibody is encoded by human heavy chain and human kappa light chain nucleic acids comprising the nucleotide sequences in their variable regions as set forth in SEQ ID NO:5 and SEQ ID NO:7, respectively.

113. (New) The antibody of Claim 103, wherein said antibody has a human heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO:2.

114. (New) The antibody of Claim 103, wherein said antibody has human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO:2 and SEQ ID NO:4, respectively.

115. (New) An isolated human monoclonal antibody which binds to an epitope on human CD20 defined by the antibody of Claim 114.

116. (New) The antibody of Claim 103, wherein said antibody has a human heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:6.

117. (New) The antibody of Claim 103, wherein said antibody has human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO:6 and SEQ ID NO:8, respectively.

118. (New) An isolated human monoclonal antibody which binds to an epitope on human CD20 defined by the antibody of Claim 116.

119. (New) The antibody of Claim 103, wherein said antibody is produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, in which V-(D)-J gene segment rearrangements have resulted in the formation of a functional human heavy chain transgene and a functional human light chain transgene, fused to an immortalized cell.

120. (New) A hybridoma comprising a B cell obtained from a transgenic non-human animal in which V-(D)-J gene segment rearrangements have resulted in the formation of a functional human heavy chain transgene and a functional light chain transgene fused to an immortalized cell, wherein the hybridoma produces a detectable amount of the monoclonal antibody of Claim 103.

121. (New) A hybridoma which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:1 and SEQ ID NO:3, respectively.

122. (New) A hybridoma which produces a human monoclonal having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences as set forth in SEQ ID NO:2 and SEQ ID NO: 4, respectively.

123. (New) The antibody of Claim 103, wherein said antibody is produced by a transfectoma comprising nucleic acids encoding a human heavy chain and a human light chain.

124. (New) A human monoclonal antibody which binds to human CD20, comprising complementarity determining region 3 (V_H CDR3) having the amino acid sequence set forth in SEQ ID NO:15, said antibody obtained by:

i) immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with a cell which has been transfected with human CD20, such that antibodies are produced by B cells of the animal;

ii) isolating B cells of the animal;

iii) fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies specific for human CD20; and

iv) isolating the human monoclonal antibodies specific for CD20 from the culture supernatant of the hybridoma, or the transfectoma derived from such hybridoma.

125. (New) An isolated human antibody comprising a heavy chain variable region amino acid sequence from a human V_H3-09/JH6b germline sequence (SEQ ID NO:56) and a light chain variable region amino acid sequence from a human V_L-L6/JK5 germline sequence (SEQ ID NO:57), wherein the human antibody binds to human CD20.

126. (New) A composition comprising the human antibody of Claim 103 and a pharmaceutically acceptable carrier.

127. (New) A composition comprising a combination of two or more human antibodies according to Claim 103, which have complementary functional activities.

128. (New) A composition comprising a first human antibody and a second human antibody, both of which bind to human CD20, wherein the first antibody has human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set

forth in SEQ ID NO:2 and SEQ ID NO:4, respectively, and wherein the second antibody has human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO:10 and SEQ ID NO:12, respectively.

129. (New) A composition according to Claim 126, further comprising a therapeutic agent.

130. (New) A kit for detecting the presence of CD20 antigen, or a cell expressing CD20, in a sample comprising the antibody of Claim 103.

131. (New) An isolated human monoclonal antibody which binds an epitope on human CD20, wherein said epitope does not contain or require the amino acid residue alanine at 170 or proline at position 172 of CD20, but includes the amino acid residues asparagine at position 163 and asparagine at position 166.

132. (New) An isolated human monoclonal antibody which binds to human CD20, comprising a heavy chain variable region and a light chain variable region, wherein said heavy chain variable region comprises complementarity determining region 3 (V_H CDR3) having the amino acid sequence set forth in SEQ ID NO:15, and wherein said antibody induces complement dependent cytotoxicity (CDC) of cells expressing CD20 in the presence of complement.

133. (New) The antibody of Claim 132, wherein said antibody:

(i) induces at least 20% CDC mediated lysis of B-CLL cells in the presence of 33 vol/vol% plasma within 3 hours at 37 °C at an antibody concentration of 10 μg/ml;

(ii) induces at least 20% lysis of B-CLL cells in the presence of 33 vol/vol% whole blood cells within 3 hours at 37 °C at an antibody concentration of 10 μg/ml;

(iii) prolongs the 50% survival rate of SCID mice injected with Daudi cells cells by more than 30% at a dose of 20 μg; or

(iv) depletes peripheral B cells expressing low levels of CD20 ($CD20^{low}$ B cells) to undetectable levels for more than 50 days in cynomolgus monkeys at a dosage of 6.25 mg/kg per day for 4 consecutive days.

134. (New) The antibody of Claim 133, wherein said antibody induces at least 20% CDC-mediated lysis of B-CLL cells in the presence of 33 vol/vol% plasma within 3 hours at 37°C at an anti-CD20 antibody concentration of 10 μg/ml.